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Dockets Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
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Re: Docket No. 2003N-0076; Food Labeling: *Trans* Fatty Acids in Nutrition Labeling; Consumer Research to Consider Nutrient Content and Health Claims and Possible Footnote or Disclosure Statements; Reopening of the Comment Period; 69 Fed. Reg. 9559 (March 1, 2004)

Dear Sir or Madam:

We are submitting these comments on behalf of our client, GFA Brands, Inc. (GFA), in response to the above-referenced Food and Drug Administration (FDA) Advance Notice of Proposed Rule Making (ANPR) on *trans* fatty acids in nutrition labeling. The agency has requested comments regarding potential approaches for establishing a daily value (DV) for *trans* fatty acids and saturated fat, qualifying criteria for nutrient content and health claims, and related issues. As explained in the material below and in testimony GFA presented to the Nutrition Subcommittee of the FDA Food Advisory Committee (FAC) on April 27, 2004, GFA believes that the agency should allow for the use of cardiovascular disease health claims and "trans fat free" claims on certain products with a healthful balanced fatty acid profile, regardless of whether the products qualify as "low" in saturated fat. This requirement should not bar claims on certain products, like GFA's buttery spreads, that have been specially designed to provide a healthy balanced ratio of fats, and, when consumed as part of a balanced diet and exercise program, are effective in improving the cholesterol profile, thus, reducing the risk of heart disease.

GFA applauds the agency's efforts to require quantitative *trans* fat labeling and to reevaluate the qualifying criteria for nutrient content and health claims in light of current recommendations for *trans* fat and saturated fat intake. GFA manufactures and markets Smart Balance, a line of products containing a patented blend of natural vegetable oils developed to help improve the cholesterol ratio (lowering "bad" low density lipoprotein, or LDL cholesterol while maintaining "good" high density lipoprotein, or HDL cholesterol) and help provide a balanced fat diet, which can reduce the risk of heart disease. Smart Balance products include buttery spreads, cheese products and other foods, as well as a total eating plan designed to provide a healthy diet with the right balance of polyunsaturates, mono-unsaturates and saturates, including Smart Balance Omega Plus, which also contains a favorable balance between Omega-6 and Omega-3 polyunsaturates. Smart Balance products contain no *trans* fat.

As FDA considers the scientific and policy issues raised in this rulemaking, GFA urges the agency to adopt a comprehensive approach that takes into account the totality of information now known about dietary fat and health. As described more fully below, the available body of evidence points to fatty acid balance as a critical factor in constructing diets that promote healthful serum lipoprotein profiles. More specifically, the evidence demonstrates that a balanced intake of the right types of saturated fatty acids (SFA or S), polyunsaturates (PUFA or P), and monounsaturates (MUFA or M) is needed to achieve the best ratios of LDL to HDL cholesterol. The scientific support for balanced fat intakes must be taken into consideration as labeling issues relating to *trans* fat and saturated fat are explored. Indeed, if the intended health benefits of the final rule on *trans* fat labeling are to be fully realized—and hopefully surpassed with benefits that may flow from future regulatory initiatives—the agency must adopt labeling policies that encourage the marketing and reformulation of products with healthful fatty acid profiles.

FDA is especially urged to exercise flexibility when considering new or revised criteria for saturated fat in nutrient content and health claims. There is significant scientific agreement supporting the use of products, like GFA's, that do not meet existing or proposed saturated fat criteria for claims such as "trans fat free," but do, more importantly, provide a balanced ratio of fats with a saturated fat: monounsaturated fat: polyunsaturated fat ratio of approximately 1:1:1 (or more specifically, 1:1.3:1). For example, GFA has extensive data establishing that the fat blend in Smart Balance Omega Plus, when consumed as part of a healthy diet and exercise program, is effective in improving the LDL/HDL cholesterol profile. To allow products such as Smart Balance Omega Plus to bear appropriate, truthful, and not misleading claims, and to promote the marketing of products with healthful fatty acid profiles, FDA should develop flexible nutrient content and health claim criteria that reflect the current state of scientific knowledge regarding the need for a balanced fatty acid intake. The final regulations, therefore, should allow the use of "trans fat free" claims on products with a balanced fatty acid profile regardless of whether the products qualify as "low" in saturated fat.

The remainder of these comments summarizes the extensive data supporting the beneficial effect of diets with a balanced fatty acid intake on the critically important LDL/HDL ratio.

Research Findings

Dr. K.C. Hayes at the Foster Biomedical Research Laboratory of Brandeis University has conducted in-depth research and written extensively on the subject of dietary fat and heart health. The information below was compiled from materials developed by Dr. Hayes.

Healthy fat intake.

Current National Cholesterol Education Plan (NCEP) and American Heart Association (AHA) Dietary Guidelines encompass the best and most relevant guide for fat and cholesterol intake. They recommend limiting fat to 30-40% of total dietary calories (%en) with the prudent recommendation at the low end because 40%en, common in the North American diet, tends to have the undesirable consequence of raising total cholesterol (TC) and LDL values. Decreasing fat to 20% or less can also be troublesome because, although LDL may decline, HDL may also fall even though triglycerides tend to rise. This combination typically leads to more dense LDL particles, likely due to the distorted balance between SFA, MUFA, and PUFA at 20%en. At this intake level, PUFA can easily become limited, thereby distorting lipoprotein (LP) metabolism and the LP profile.

Fatty acid balance.

The original AHA Step I diet fat recommendations recognized the significance of the fatty acid balance at approximately 1:1:1 for SFA:MUFA:PUFA. Careful review of numerous published reports has revealed the importance of this balance in generating the best LDL/HDL ratio. Furthermore, the balance appears to be critical at any level of fat intake if one wishes to avoid adversely affecting the LP profile.

Within the concept of "balance" among classes of fatty acids, certain specific fatty acids have been found to be more beneficial than others. Many studies have suggested that SFA raise TC, LDL, and HDL and that PUFA lower them, but certain SFA (as consumed in the diet) are better in terms of their impact on the LDL/HDL ratio than others. Fats rich in 12:0+14:0 (milk fat, coconut oil, palm kernel oil) raise LDL the most. Stearic acid (18:0) is not prevalent in saturated fats, but it is neutral in its effect on blood cholesterol when consumed in natural fats. The most common SFA is palmitic acid (16:0), (so named because it represents the major SFA in palm oil). The 16:0 SFA is present to some degree in essentially all fats and is by far the most prevalent SFA in our diets. Considering the influence on the LP profile, 16:0 is intermediate, i.e., it can be neutral when placed on a triglyceride molecule with MUFA, PUFA or 18:0, or cholesterol-raising when attached along with 12:0+14:0. In high amounts 16:0 can even raise TC and LDL when substituted for 18:0 MUFA, or

PUFA in people who already have elevated TC or who eat large amounts of cholesterol. Accordingly, the general advice has been to remove as much SFA from the diet as possible. This is often not practical because the manufacture of many food products requires SFA, or some facsimile thereof, such as trans fatty acids. Moreover, extreme removal of dietary SFA is not recommended because their deletion from the diet surprisingly exerts an adverse effect on the LDL/HDL ratio.

What is the best approach to saturated fats? In recent years, one mistaken answer has been to utilize synthetic SFA manufactured by "hardening" vegetable oils through hydrogenation. This process makes a stiff, plastic fat this is rich in so-called trans fatty acids (TFA). However, studies now show that these TFA can be worse than any of the individual natural SFA because they not only raise LDL but also lower HDL, leading to an exaggerated increase in the LDL/HDL and in cardiovascular risk. TFA also increase a highly atherogenic lipoprotein in the LDL fraction called Lp(a). An alternative to the harmful effects of TFA is to provide a reasonable level of SFA in our diet by careful selection of naturally available SFA. Brandeis University's research with monkeys and humans indicates that the guidelines are best tempered by the original AHA Step I diet (30%en from dietary fat and 1:1:1 for SFA:MUFA:PUFA) and that the best SFA are 16:0 and 18:0 from *natural* fats. This conclusion comes from carefully analyzing all aspects of the NCEP-AHA recommendations coupled with analysis of the available LP data in relevant studies involving the controlled intake of dietary fat in humans (and experimental animals).

What is the best approach to PUFA? In selecting PUFA, the issue of whether to include linoleic acid (18:2n-6) or linolenic acid (18:3n-3), or longer n-3 like EPA and DHA, must be considered. Both n-6 and n-3 families are essential fatty acids (needed in the diet because the body cannot synthesize them) and both are important to health, especially cardiovascular health. The linoleic acid (n-6) level has the greatest impact on regulating the LDL/HDL ratio, whereas linolenic acid (n-3) and its longer derivatives have a major influence on clotting mechanisms, as well as stabilizing the heart against abnormal beating, called arrhythmias, that can lead to sudden death. Diets enriched in 18:3n-3, or even better, 22:6n-3 (DHA) have been shown to exert a significant anti-coronary heart disease effect in humans, both in clinical and epidemiological studies. Smart Balance® contains a good balance (7:1) of linoleic (n-6) to (n-3) linolenic acids. This balance is unlike partially hydrogenated margarines, in which most of the linolenic acid has been destroyed by processing, and is also unlike most vegetable oils, which contain only a small amount of this important fatty acid (soybean and canola oils being exceptions).

Dietary Cholesterol.

Dietary cholesterol is very important in the equation, as evidenced by the NCEP-AHA diet recommendations to reduce daily intake below 300mg or even 200mg, depending on individual risk. In fact, dietary cholesterol increases the body's sensitivity to SFA, so that maximizing its removal can substantially reduce much of the negative influence of SFA on the LP profile. Polyunsaturated fatty acids, on the other hand, are the major fatty acid able to actually offset the negative impact of dietary cholesterol because linoleic acid (18:2n-6) increases the removal of plasma LDL, the main LP that is increased by dietary cholesterol.

Monounsaturates.

From the Brandeis researchers' results and the analysis of others, monounsaturated fatty acids have been found to be essentially neutral in terms of the LP profile, and thus, perhaps, are the best source of fatty acids to use as extra "filler" in the dietary fat load. Nevertheless, the critical issue is how much SFA and PUFA should be consumed to achieve the best LDL/HDL ratio. As Hayes' comparison between olive oil and balanced fat revealed in cynomolgus monkeys, a high MUFA intake at the expense of PUFA and SFA does not counter the presence of dietary cholesterol very well and leads to an increased LDL/HDL ratio relative to a balanced SFA:MUFA:PUFA ratio that allows for a higher PUFA intake. Thus, for example, fat blends like Smart Balance® incorporate a better fatty acid balance than olive oil alone.

The LDL/HDL Ratio.

An elevated cholesterol level (TL >180mg/dl, LDL >110mg/dl) begins to increase risk for coronary heart disease (CHD). Most of any increase above 180mg/d arises in the LDL pool, and this lipoprotein is the one that is deposited during arterial cholesterol build-up. On the other hand, people (and essentially all animals) with naturally high levels of HDL do not develop CHD, primarily because this lipoprotein transports cholesterol back to the liver for excretion in bile. HDL in the arterial wall also blocks LDL deterioration, thereby preventing the local damage induced by LDL accumulation. Thus, the "bad" and "good" cholesterol connotations for these two LPs become apparent and the justification for maintaining the lowest LDL and highest HDL (i.e. best LDL/HDL ratio) possible for any given TC value.

The Brandeis-PORIM research and GFA products.

A novel finding from collaborative nutritional research at Brandeis University and the Palm Oil Research Institute of Malaysia (PORIM) resulted in technology to produce fat blends free of trans fatty acids and a Brandeis patent that was licensed to GFA Brands. The patent defines a means to produce the 1:1:1 balance in fatty acids recommended for many years by the AHA and adjusted by trial and error to approximately 1:1.3:1 through Brandeis-PORIM experiments and product development by GFA. Adequate intake of natural fats blended to approximate this fatty acid balance consistently elicits the best LP profile in animals and humans. This seems to be true for all levels of fat intake normally consumed in Western diets (20-40% of total calories). Significant deviation from a balanced ratio between SFA:MUFA:PUFA, such as too low SFA or too high MUFA or PUFA, induces a less than ideal LP profile, even if the total plasma cholesterol is lower.

Licensing of the Brandeis–PORIM technology by GFA Brands, Inc., resulted in Smart Balance® / Earth Balance margarines and a family of related products for use in a total diet program specifically designed to approximate this 1:1.3:1 fatty acid balance from blends of natural oils, thereby removing all trans fatty acids. Several human studies and epidemiologic reports indicate that trans fatty acids are more harmful than the saturated fatty acids they were designed to replace. In fact, some of the deleterious effects attributed to saturated fatty acids over the years were probably the result of their substitution by trans fatty acids; when assessed by direct comparison with specific fatty acids, trans fatty acids proved worse than the saturated fatty acids they were designed to replace.

Substantiation from Studies & Reports

The following conclusions are made in published reports and studies, described below, which provide substantiation for the information contained in our comments.

- **Fatty acid balance is more critical than the amount of fat.** 1/

This report evaluated the importance of dietary fatty acid balance on the lipoprotein profile in 22 nuns (aged 22-55, mostly post-menopausal) who had mildly elevated TC (224mg/dl at entry). They were fed three dietary fats for 6 weeks each: first, a high-level, saturated fat (42%en, P/S= 0.16); or second, that same level of fat with a balanced fatty acid profile (P/S, 1.0), which was accomplished by decreasing SFA (exact fatty acid profile not provided) and increasing PUFA. The third fat was close to the original AHA Step I (32%en with a 1:1:1 balanced fatty acid profile) and similar to the S:M:P balance in the second fat rotation. The results suggest that if one begins

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1/ Weisweiler, P., Janetschek, and Schwandt, P., *Influence of polyunsaturated fats and fat restriction on serum lipoproteins in humans,* Metabolism 34, 83-87 (1985).

with a very unfavorable PUFA/SFA ratio (only 0.16 because PUFA was too low) in a high-fat diet (42%en), balancing the P/S ratio along AHA guidelines improves TC and the LDL/HDL ratio. (*See* Fig. 4.) The new balance between SFA and PUFA decreased LDL and increased HDL slightly.

However, dropping fat intake to 32%en with the AHA balance in place did not improve TC or the LDL/HDL ratio further. Significantly, in the 30-40%en range, a balance (adequate PUFA, adequate SFA) seems more critical than total fat. Although the exact SFA profile was not described, other studies have found that decreasing 12:0+14:0 is more important than decreasing 16:0+18:0 if the best LDL/HDL ratio is to be achieved at a lower SFA intake. 2/ Thus, the approximately equal balance of S:M:P (1:1.3:1) as recommended by NCEP-AHA is an important basic consideration *at any fat intake* for maintaining the best LDL/HDL ratio.

- **Both SFA and PUFA are required for the best LDL/HDL ratio.** 3/

This report tested the hypothesis that providing either too few SFA or PUFA in the diet (i.e. an imbalance between them) would be detrimental to the HDL or LDL level, respectively. Three fats were fed in whole-food diets, providing 2/3 of the daily fat load from the supplemented oil in each diet (with 31% of daily calories as fat) for 23 young men with normal cholesterol values. The diet fat was initially balanced as AHA Step I recommends with a 10:13:8 ratio of SFA:MUFA:PUFA in the final diet followed by a high-MUFA, low-SFA (6:17:8) or a high-SFA, low-PUFA (13:14:4) diet. The first fat represented a blend of soybean oil:palm oil:canola oil, whereas the other two fats were supplied as canola oil or palm olein alone. All three fats produced about the same normal total cholesterol value, but the AHA blend produced the highest HDL and lowest LDL, so that the LDL/HDL ratio was significantly enhanced by the AHA balanced blend of SFA:MUFA:PUFA. (*See* Fig. 1.) Thus, neither too low SFA nor too low PUFA was adequate, and MUFA were no substitute for either. Rather, one needs a balance of PUFAs (to lower LDL) and SFA (to raise HDL) for the best TC and LDL/HDL profile, at least when following an AHA Step I diet at 30%en from fat. The 9:12:9 balance for SFA:MUFA:PUFA inherent in the current NCEP and AHA recommendations for 30%en from fat appears to be the best advice for the average individual.

2/ *See infra* n.13.

3/ Sundram, K., Hayes, K. C. and Siru, O. H., *A balance between dietary 18:2 and 16:0 may be required to improve the serum LDL/HDL cholesterol ratio in normocholesterolemic me,* J.Nutr. Biochem. 6,179-87 (1995).

- **Fatty acid balance selectively lowers LDL but not HDL.** 4/

This report addressed the issue of whether simply improving the fatty acid balance in the diet of 30 normolipemic men fed a typical Western diet fat intake (37%en) would enhance the lipoprotein profile, even after 3 months of comparison feeding and even if not including the typical goal of reducing fat intake to 30%en. The hypothesis was tested by switching from a P/S fatty acid ratio of 0.3 to a ratio of 1.0, thus adopting an AHA balance in S:M:P of 1:1.3:1. The average entry TC was upper-normal (200mg/dl), and the level of PUFA intake (5.6%en) is very typical of the U.S. today. Balancing the P/S to 1.0 by shifting 6%en from SFA to PUFA caused a significant decline in TC and LDL without depressing HDL. (*See* Fig. 3). This resulted in significant improvement in the LDL/HDL ratio. A design flaw was the failure to designate the specific type(s) of SFA removed. Thus, similar to a subsequent trial5/, balancing the dietary fatty acid intake over a significant period of time is beneficial. Balancing fatty acid is important if one wants to lower LDL without depressing HDL, even when consuming a somewhat elevated level of dietary fat (37%en) in normolipemic subjects.

- **Too high PUFA or too low fat depresses both LDL and HDL.** 6/

This report demonstrates what happens to LDL and HDL in normolipemic (n=11) and hyperlipemic (n=19) subjects fed a very saturated, high-fat diet (P/S 0.2, 40%en) or a very polyunsaturated, high-fat diet (P/S 2.0, 40%en). Subjects were then compared to an almost fat-free saturated fat diet (P/S 0.2, 3%en). Two questions were addressed: (1) Does the response of people with normal cholesterol differ from those with high cholesterol? and (2) Does the LDL/HDL profile benefit more from a high polyunsaturated fat approach to diet modification or is it better to drastically reduce the fat intake by eating a high-carbohydrate (low-fat) diet without concern for the fatty acid balance?

4/ Schwandt, P., Janetschek, P., and Weisweiler, P., *High density lipoproteins unaffected by dietary fat modification*, Atherosclerosis 44, 9-17 (1982).

5/ *See supra* n.3.

6/ Schaefer, E.J., Levy, R.I., Ernst, N.D., Van Sant, F.D., and Brewer, H.B. *The effects of low-cholesterol, high-polyunsaturated fat, and low fat diets on plasma lipid and lipoprotein cholesterol levels in normal and hypercholesterolemic subjects*, Am. J. Clin. Nutr. 34, 1758-1763 (1981).

The results show that a high-PUFA diet (P/S 2.0) decreased both LDL and HDL in all subjects. (*See* Fig. 5.) Removing essentially all the fat (low-fat) decreased both LDL and HDL even further. The LDL/HDL ratio did not improve with either tactic and the general response was similar for both groups of subjects, i.e. normolipemics and hyperlipemics. Thus, a very high-PUFA or an essentially fat-free diet will both decrease TC and LDL in both normolipemic and hyperlipemic subjects, but the decline in HDL is also substantial. The LDL/HDL ratio does not improve. As shown, if one wishes to maintain the HDL while selectively lowering LDL and thereby improve the LDL/HDL ratio, a balance between dietary SFA and PUFA is important. The same decrease in LDL obtained with very high PUFA can be achieved by simply balancing S:M:P, and this balanced approach does not depress HDL.

- **Fatty acid balance is especially critical in low-fat diets.** 7/

The objective of this study was somewhat similar to the Jones study 8/, emphasizing the importance of balance at any level of fat intake. Specifically, it determined whether the TC and lipoprotein profile would be altered by decreasing fat intake from a high level (39%en) to a low level (22%en) if the P/S ratio were held constant and balanced at about 1.0. Most studies show that switching to a high-carbohydrate (low-fat) diet lowers TC, including both LDL and HDL. 9/ Nine normolipemic males were evaluated in a carefully monitored metabolic ward, but the S:M:P ratios were not totally balanced and were 1.2:1.5:1.0 (hi-fat) and 1:1.4:1 (low-fat), providing P/S ratios of 0.8 and 1.0, respectively. The results reveal that the TC, LDL, and HDL were not significantly affected by the fat load, although they tended to be slightly lower during the low-fat period without affecting the LDL/HDL ratio. (*See* Fig. 6.) Thus, a low-fat diet (22%en) does not necessarily mean that HDL will decline during a high carbohydrate intake, provided that the balance between SFA and PUFA is maintained. However, the tendency toward slightly lower HDL at 22%en suggests that 30%en from fat might better sustain HDL 10/ or that the MUFA intake was allowed to drift up too far relative to SFA and PUFA for this low fat intake.

7/ Nelson, G.J., Schmidt, P.C., and Kelley, D.S., *Low-fat diets do not lower plasma cholesterol levels in healthy men compared to high-fat diets with similar fatty acid composition at constant caloric intake,* Lipids 30, 969-976 (1995).

8/ *See infra* n.17.

9/ *See supra* n.8.

10/ As shown in the Sundrum study. *See supra* n.5.

The results suggest that the dietary P/S ratio is important at any fat intake, but is especially critical for maintaining the best LP profile during low-fat intake (<20-25%en) because it dictates the absolute intake of 18:2. At low-fat intakes, a low P/S ratio (<0.5) greatly limits the 18:2 needed to meet metabolic requirements for normal LP metabolism, especially for lowering the LDL, but also for sustaining HDL. As pointed out in other references, a dietary S:M:P ratio of 1:1.3:1 generally appears to be best.

- **Progressive removal of SFA lowers both LDL and HDL.** 11/

This carefully executed first DELTA study examined the effect of a two-step selective removal of SFA (at 4.5%en each step) from a human diet containing 34%en as fat, while keeping MUFA and PUFA constant. Even though the P/S ratio increased to 1.0 in the process, MUFA intake equaled the other two fatty acid classes combined in the low-fat diet (containing 25%en as fat). This progressive removal of 9%en as SFA decreased LDL by 12%, but HDL was depressed proportionally. (*See* Fig. 10.) Thus, the indiscriminant removal of SFA (individual SFA not identified) lowers TC without improving the LDL/HDL ratio, at least when MUFA intake substantially exceeds that of SFA or PUFA.

- **SFA are best represented by 16:0 and 18:0.** 12/

The most recent NCEP and AHA diets recommend a fat intake of about 30%en with a balance of approximately 7:15:8 %en for S:M:P. As indicated by the Mustad study above, this fat profile typically means reducing SFA in the average diet, but does it matter which of the major 4 SFA are removed? The Brandeis/Hayes' study data from cebus and rhesus monkeys reveal that removal of fats containing 12:0+14:0 (leaving 16:0+18:0-rich fats) leads to a greater reduction in TC and LDL and results in a better LDL/HDL ratio, especially if the overall fatty acid profile is balanced instead of

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11/ Mustad, V.A., Etherton, T.D., Cooper, A.D., Mastro, A.M., Pearson, T.A., Jonnalagadda, S.S., and Kris-Etherton, P.M., *Reducing saturated fat intake is associated with increased levels of LDL receptors on mononuclear cells in healthy men and women,* J. Lipid Res. 38:459-468 (1997).

12/ Pronczuk, A., and Hayes, K.C., *Ideal LDL/HDL ratio requires precise balance in dietary saturated and polyunsaturated fatty acids in cebus monkeys,* FASEB J. 6: A561 (1999); Khosla, P., Hajri, T., Pronczuk, A. and Hayes, K.C., *Decreasing dietary lauric and myristic acids improves plasma lipids more favorably than decreasing dietary palmitic acid in rhesus monkeys fed AHA Step 1 diets,* J. Nutr. 127:525S-530S (1997).

simply removing the SFA. (*See* Fig. 9.) The preference for 16:0+18:0 reflects the fact that 12:0+14:0-rich fats tend to increase LDL more than HDL. Thus, when balancing the S:M:P ratio in a fat blend, it is preferable to utilize a natural 16:0+18:0-rich fat (e.g. palm oil, beef tallow) rather than one rich in 12:0+14:0 (e.g. milk fat, coconut oil, palm kernel oil) in terms of generating the best LDL/HDL ratio.

- **Trans fatty acids are worse than saturated fatty acids in humans.** 13/

Trans fatty acids are generated when vegetable oils are hardened by hydrogenation in order to replace naturally saturated fat in the diet. Since they typically are monounsaturated, it was thought that trans exerted a neutral effect on cholesterol metabolism and other biological functions. However, more recent data suggests that they have a negative influence on lipoproteins and possibly other functions, as well.

To examine this point more directly, trans 18:1n9 (elaidic acid) was compared head-to-head with the most cholesterol-raising saturated fatty acids and the neutral, cis 18:1n9 (oleic acid) in humans. The four fats representing these fatty acids were tested in natural diets of normocholesterolemic subjects who each consumed all 4 diets over a 16-week period. The data reveal that trans fatty acid proved as cholesterol elevating as the worst SFA (12:0+14:0), and that trans had the most detrimental impact on LDL (greatest increase) while uniquely depressing HDL. (*See* Fig. 13.) Again, note that the 16:0-rich fat was neutral and comparable to the cis18:1-rich fat. Thus, when assessed by direct comparison with specific fatty acids, trans fatty acids proved worse than the saturated fatty acids they were designed to replace.

- **High MUFA is not as favorable as a low MUFA diet.** 14/

The original AHA recommendation called for an even balance between S:M:P at 30%en from fat. Recently, AHA has recommended approximately 50% more MUFA at the expense of SFA and PUFA, especially as fat intake rises above 30 %en. However, a human study in 8 normolipemic males demonstrates the potential downside of exaggerating the M:P ratio, feeding either 0.5 or 3.0 M:P ratios in two diets in which

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13/ Sundram, K., Ismail, A., Hayes, K.C., *Trans (elaidic) fatty acids adversely affect the lipoprotein profile relative to specific saturated fatty acids in humans*, J.Nutr. 127:514s-520s (1997).

14/ Chang, N.W. and Huang, P.C., *Effects of dietary monunsaturated fatty acids on plasma lipids in humans*, J. Lipid Res. 31, 2141-2147 (1990).

the P/S ratio would be considered ideal and constant at 1.0. The high-MUFA diet produced a TC that was identical to the low-MUFA diet, but the LDL was elevated ($p<0.05$) when SFA and PUFA intake became too low; the HDL was also lower (n.s.), so that the LDL/HDL ratio was significantly increased by high MUFA. (*See* Fig. 8.) In addition, the high-MUFA diet induced a 20% rise in triglycerides. Thus, the high-MUFA diet proved inferior to the low-MUFA intake, indicating that a proper balance of all three fatty acid classes (S:M:P) is important for generating the best LDL/HDL ratio. Even though keeping the P/S ratio about 1.0 may be the most critical relationship, it would appear that MUFA should not exceed 1.5 times their relative abundance of PUFA and SFA.

- **High MUFA is inferior to a balanced S:M:P fatty acid ratio.** 15/

The objective of this study in cynomolgus monkeys more precisely explored the relative importance of the S:M:P balance in the regulation of TC and LDL/HDL ratio when consuming 30%en and less than 300mg/day cholesterol human equivalent (i.e. AHA Step I diets). Similar to the human results just cited 16/ and compared to an American fat blend derived from butter and canola oil, an unfavorable imbalance developed in the LDL/HDL ratio when dietary SFA and PUFA were about equal, but too low relative to MUFA. (*See* Fig. 9.) Specifically, AHA Step I diets (Diets 1X and 1H) with P/S ratios close to 1.0 represented blends of four and three oils, respectively. The third test diet was olive oil alone with a fairly favorable P/S ratio of 0.75. The TC response, as well as the LDL/HDL ratio, were much improved when the relative intake of S:M:P was fully balanced in the two AHA diet blends. Thus, while the dietary P/S ratio is a rough indicator of how a fat will affect the plasma LDL/HDL ratio, it would appear that an approximate balance between all three fatty acid classes (S:M:P) is also critical, at least at 30%en fat intake.

- **HDL can increase when total fat intake decreases.** 17/

It is generally agreed that replacing fat with carbohydrate is associated with a decline in TC, but HDL also tends to decrease. In retrospect, one of the first

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15/ Hayes, K.C. et al., *Lipoprotein response of cynomolgus monkeys fed AHA Step I diets having different fatty acids profiles* (unpublished data).

16/ *See supra* n.10.

17/ Hjermann, I., Enger, S.C., Helgeland, A., Holme, I., Leren, P. and Trygg, K, *The effect of dietary changes on high density lipoprotein cholesterol: The Oslo Study,* Am. J. Med. 66:105-109 (1979).

studies to show that this need not occur was a subgroup from the Oslo Study, which basically applied the AHA Step I diet approach to a large population. In actual practice, reductions in total fat, especially saturated and monosaturated, and dietary cholesterol to slightly less than 30%en and less than 300mg/day, respectively, greatly reduced TC and LDL without decreasing HDL in 18,000 men. To examine this response more closely, 23 diet-responders from the original study were subsequently compared with 23 controls who continued to eat the high-fat baseline diet. Both groups had identical, elevated blood lipid values initially. The test group was taught how to lower dietary fat from 44%en to about 30%en by focusing on removal of saturated fat. In the process, a good balance in S:M:P was achieved, decreasing from an imbalanced 18:19:7 to 8:12:8 %en. The data demonstrate sharp declines in TC, LDL and TG (200 vs. 129 mg/dl) with an equally robust *increase* in HDL (42 vs. 50mg/dl). (*See* Fig. 7.) Thus, removing both SFA and MUFA from a high-fat diet to improve the overall FA balance can decrease LDL sharply, but may also increase HDL if the P/S ratio approximates 1.0 and total balance S:M:P approximates 1:1.3:1.

- **PUFA intake is critical for the best LDL/HDL ratio.** 18/

Another study addressed two questions: 1) whether a low-fat diet (20% fat calories) would improve relatively normal TC values in 31 adult women, and 2) whether it matters much if dietary fatty acids are balanced between SFA:MUFA:PUFA in either a high-fat (40% en) or a low-fat (20%en) diet situation, i.e. considerably above or below the AHA Step I diet objective of 30% fat energy, and with or without the 9:12:9 balance in S:M:P which an AHA diet would support. Several results were apparent. (*See* Fig. 2.) The dietary P/S ratio was only 0.3 in group I (n=15) and 1.0 in group II (n=16) women. Fatty acid balance had little effect on LDL or HDL at 40%en, primarily because the basal (group I) intake of PUFA (6%en) was close to the amount of 18:2 required for normal lipoprotein (LP) metabolism given the circumstances of these normolipemic women. But the superior balance (P/S 1.0) did tend to improve the LDL/HDL ratio slightly at this high-fat intake. However, when consuming the low-fat diet, balance in fatty acids was especially important because a balanced 1:1:1 ratio (group II) prevented the substantial decline in HDL seen with group I, where the typical American Fat imbalance (P/S, 0.3) resulted in higher LDL and lower HDL with a much improved LDL/HDL ratio. The undesirable impact on LDL and HDL in group I occurred primarily because the absolute intake of PUFA (at 3%en) was too low for adequate lipoprotein metabolism when total fat supplied only 20%en. Thus, the

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18/ Jones, D.Y., Judd, J.T., Taylor, P.R., Campbell, W.S. and Padmanabhan, P.N, *Influence of caloric contribution and saturation of dietary fat on plasma lipids in premenopausal women,* Am. J. Clin. Nutr.45, 1451-6 (1987).

LDL/HDL ratio was much improved by feeding the 1:1:1 fatty acid balance at the low-fat intake (group II) because the 6%en from PUFA was now adequate in absolute terms (in total grams of 18:2/day).

Accordingly, with dietary fat somewhere between 40%en and 20%en a proper balance in fatty acid intake becomes exceedingly important for generating an optimal LDL/HDL ratio, i.e. the lowest LDL and highest HDL values. Like the 1995 Sundram study 19/, it would appear that a controlled intake of PUFA (18:2) is required to allow for the greatest decline in LDL without also lowering HDL. The particular type of SFA fed in this study was not specified, although an amount of total SFA equal to the PUFA resulted in a very favorable LDL/HDL response.

* * * * *

We urge FDA to consider the above information and other available science in designing a balanced, comprehensive policy that will encourage the development and marketing of products with healthy fatty acid profiles. GFA Brands appreciates your consideration of this issue and looks forward to working with the agency in the future. We would be happy to further discuss with FDA staff any of the points made in these comments.

Sincerely,

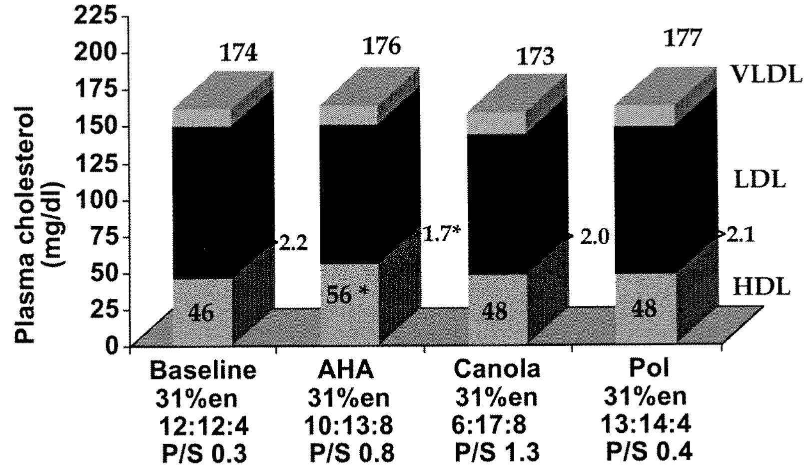
Martin J. Hahn

Enclosures

19/ *See supra* n.4.

FIG 1

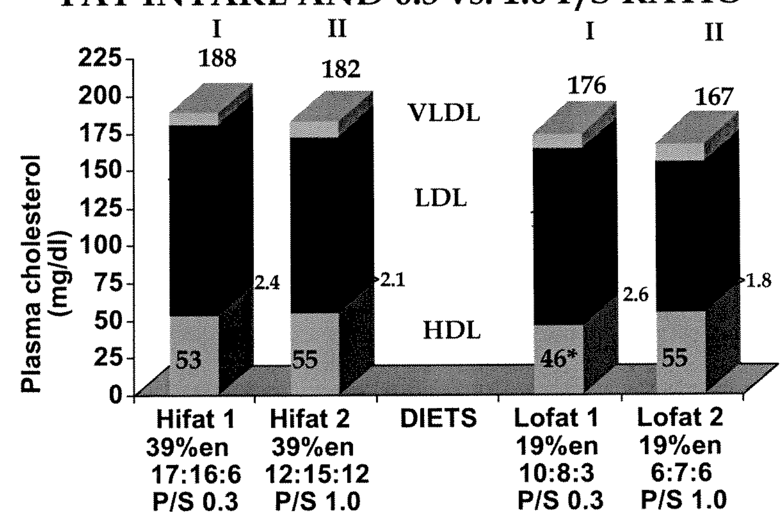
FATTY ACID BALANCE IMPROVES THE LDL/HDL RATIO IN NORMOLIPEMIC HUMANS



Sundram et al. J.Nutr.Biochem. 6:179,1995

FIG 2

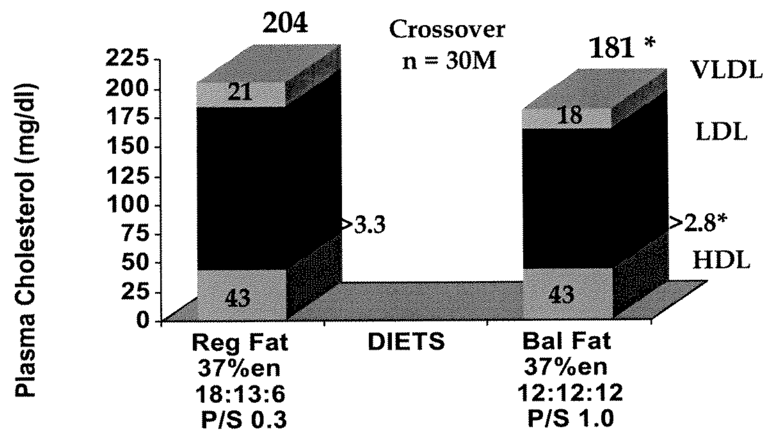
LP PROFILE IN WOMEN AT HIGH vs. LOW FAT INTAKE AND 0.3 vs. 1.0 P/S RATIO



Jones et al AJCN 45:1451,1987

FIG 3

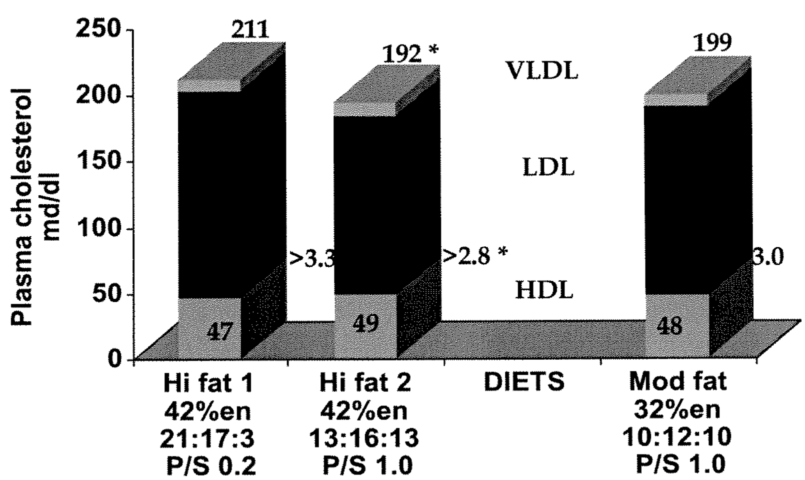
IMPROVED LIPOPROTEIN PROFILE AFTER BALANCING THE DIETARY S:M:P RATIO



Schwandt et al. ATHERO 44:9,1982

FIG 4

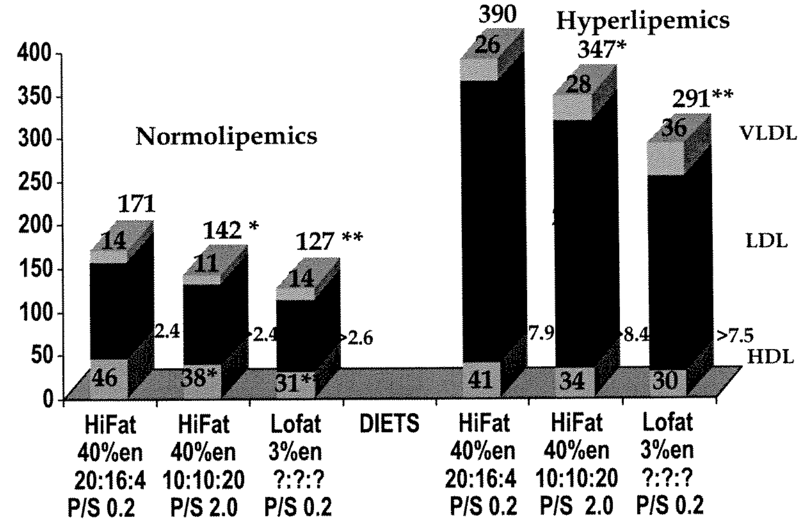
LIPOPROTEIN PROFILE AFTER HIGH vs. MOD FAT INTAKE AT TWO P/S RATIOS



Weisweiler et al. METAB 34:83,1985

FIG 5

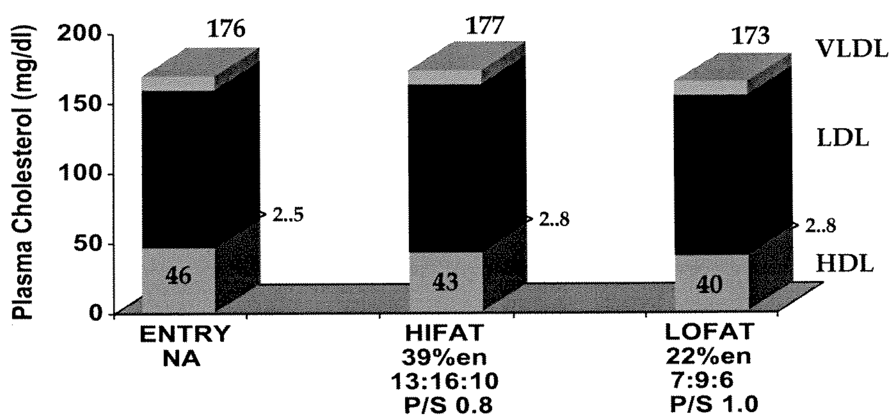
LP PROFILE IN NORMO - vs. HYPERLIPEMIC SUBJECTS AT HIGH vs. LOW P/S RATIOS



Schaefer et al. AJCN 34:1758,1981

FIG. 6

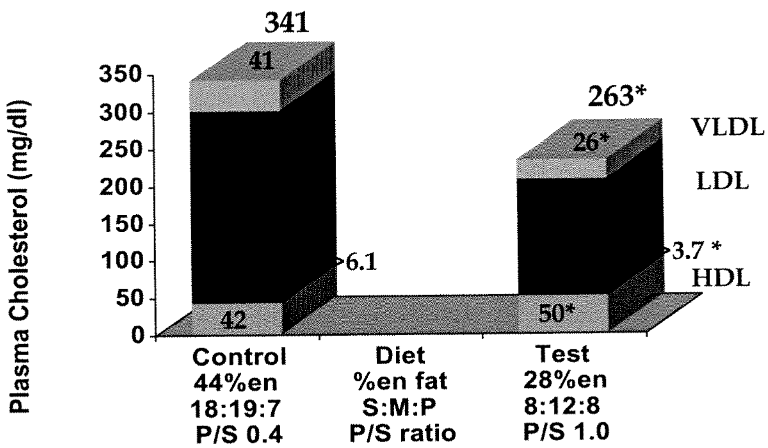
LIPOPROTEIN RESPONSE TO BALANCED FA INTAKE IN NORMOLIPEMIC MEN



Nelson et al LIPIDS 30: 969,1995

FIG 7

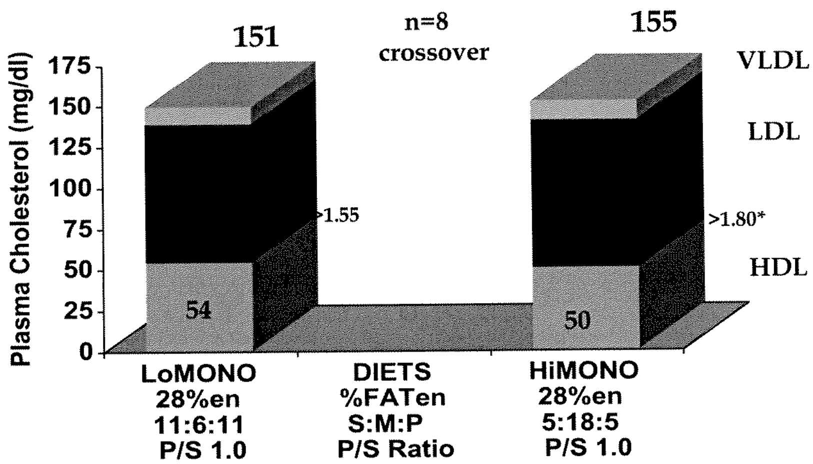
AHA STEP I DIET IMPROVES THE LIPOPROTEIN PROFILE OF HYPERCHOLESTEROLEMIC MEN



Oslo Study. Am J Med 66:105,1979

FIG. 8

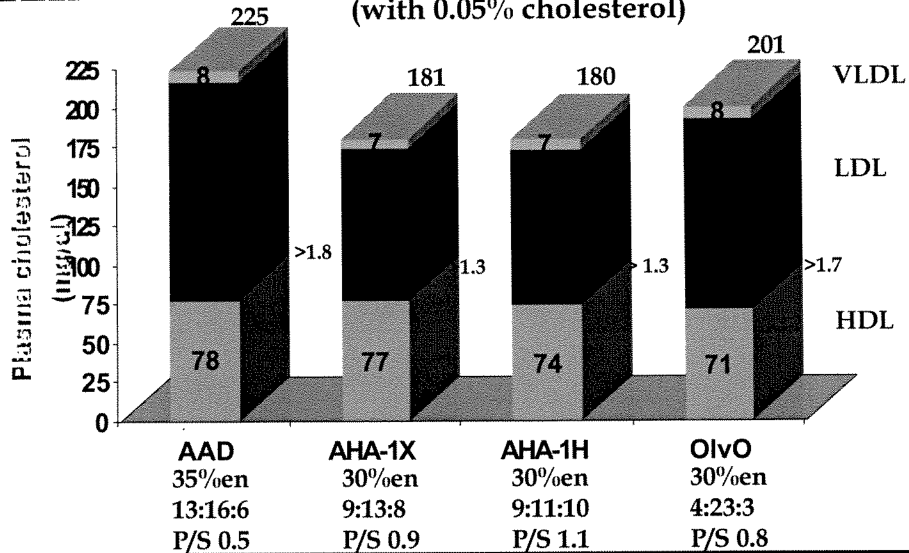
HUMAN LIPOPROTEIN RESPONSE TO A LOW-MONO OR HIGH-MONO DIET



Chang JLR 31:2141,1990

FIG 9

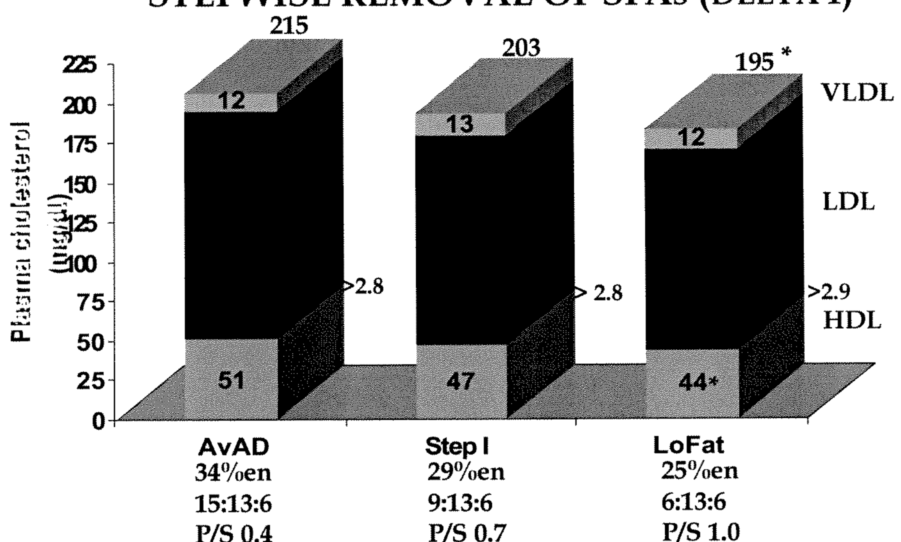
CYNO MONKEY RESPONSE TO DIETARY FA BALANCE (with 0.05% cholesterol)



Hayes, unpublished data

FIG 10

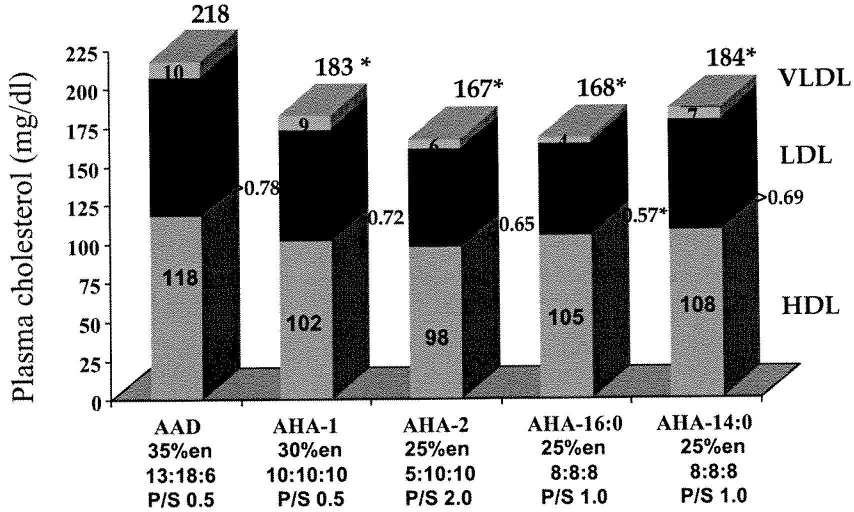
HUMAN LIPOPROTEIN RESPONSE TO STEPWISE REMOVAL OF SFAs (DELTA 1)



Mustad et JLR 38:459,1997

Fig 11

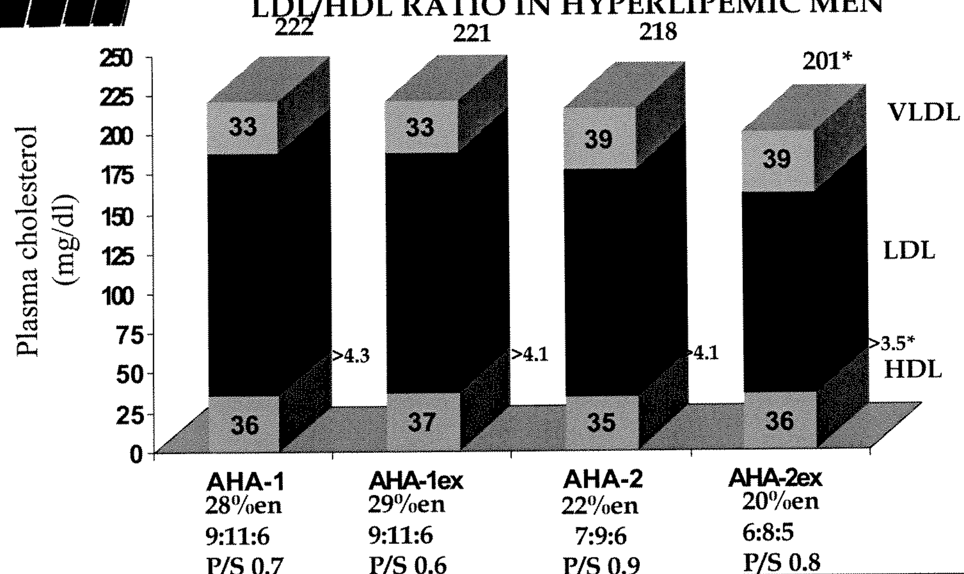
SFA and PUFA balance enhances the LDL/HDL RATIO and 16:0+18:0 are better than 12:0+14:0 in CEBUS MONKEYS



Pronczuk et al. FASEB J 6:A561,1999

Fig 12

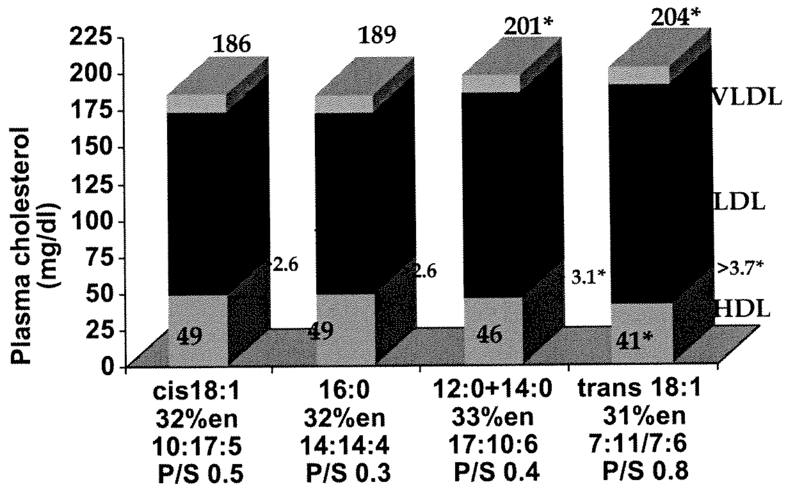
EFFECTS OF EXCERCISE AND STEP 2 DIET ON LDL/HDL RATIO IN HYPERLIPEMIC MEN



Stefanick et al. NEJ Med 339:12,1998

FIG.13

COMPARISON BETWEEN *cis* 18:1, 16:0, 12:0+14:0, AND *trans* 18:1 IN NORMOLIPEMIC HUMANS



Sundram et al. J.Nutr.127:514s,1997